

Triazole-Modified Calix[4]crown as a Novel Fluorescent On–Off Switchable Chemosensor

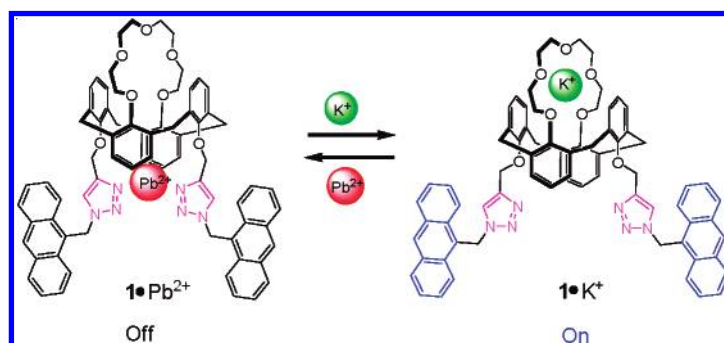
Kai-Chi Chang, In-Hao Su, Annamalai Senthilvelan, and Wen-Sheng Chung*

Department of Applied Chemistry, National Chiao-Tung University, Hsinchu, 30050, Taiwan, Republic of China

wschung@cc.nctu.edu.tw

Received June 6, 2007

ABSTRACT



A novel fluorescent on–off switchable chemosensor **1** with two different types of cationic binding sites is synthesized, which is composed of a triazole-modified calix[4]crown in the 1,3-alternate conformation. Among 15 metal ions examined, the fluorescence of **1** was strongly quenched by Hg²⁺, Cu²⁺, Cr³⁺, and Pb²⁺; however, the revival of emission from the strongly quenched **1**·Pb²⁺ complex was achievable by the addition of K⁺, Ba²⁺, or Zn²⁺ ions. Thus, metal ion exchange can trigger an on–off switchable fluorescent chemosensor.

The design and synthesis of fluorescent chemosensors with desirable properties is of considerable current interest in supramolecular chemistry.¹ Most calix[4]arene-based fluorescent sensors have been designed based on photophysical changes upon metal ion binding and their mechanisms include photoinduced electron transfer (PET),² photoinduced charge transfer (PCT),³ formation of monomer/excimer,⁴ and energy transfer.⁵ Calix[4]crowns offer particular promise because the function of calix[4]arene and crown units is

bridged through entities which enable the divergent orientation of cavities of a size and nature sufficient to accommodate a variety of guests.⁶ Recently Kim and co-workers reported an elegant synthesis of 1,3-alternate calix[4]crown as a ditopic fluorescence sensor, where the two pyrene amido groups represent one of the cationic binding sites and the crown-ether moiety represents the other. The calix[4]crown showed a strong excimer emission when free in solution,

(1) (a) Czarnik, A. W. *Chem. Biol.* **1995**, *2*, 423. (b) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515. (c) de Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coord. Chem. Rev.* **2000**, *205*, 41. (d) *Molecular Fluorescence*; Valeur, B., Ed.; Wiley-VCH: Weinheim, Germany, 2001.

(2) (a) Aoki, I.; Sakaki, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1992**, 730. (b) Bu, J.-H.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2004**, *6*, 3301.

(3) (a) Leray, I.; Lefevre, J.-P.; Delouis, J.-F.; Delaire, J.; Valeur, B. *Chem. Eur. J.* **2001**, *7*, 4590. (b) Kim, S. K.; Bok, J. H.; Bartsch, R. A.; Lee, J. Y.; Kim, J. S. *Org. Lett.* **2005**, *7*, 4839. (c) Choi, J. K.; Kim, S. H.; Yoon, J.; Lee, K.-H.; Bartsch, R. A.; Kim, J. S. *J. Org. Chem.* **2006**, *71*, 8011.

(4) (a) Jin, T.; Ichikawa, K.; Koyana, T. *J. Chem. Soc., Chem. Commun.* **1992**, 499. (b) Kim, S. K.; Lee, S. H.; Lee, J. Y.; Lee, J. Y.; Bartsch, R. A.; Kim, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 16499. (c) Schazmann, B.; Alhashimy, N.; Diamond, D. *J. Am. Chem. Soc.* **2006**, *128*, 8607.

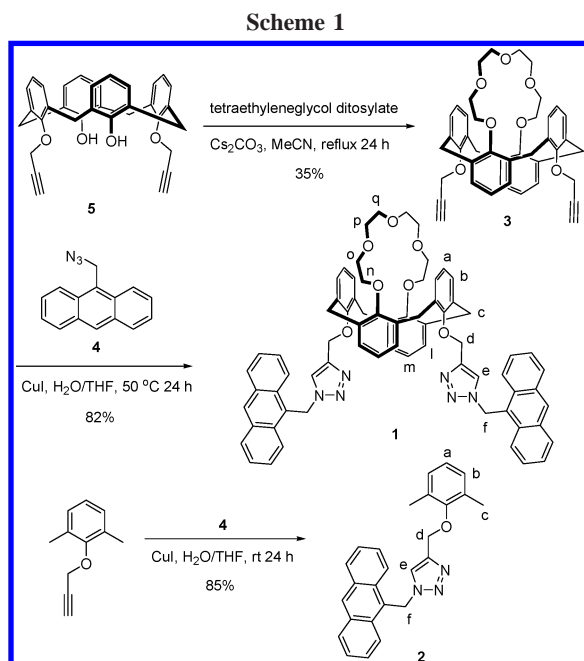
(5) (a) Jin, T. *Chem. Commun.* **1999**, 2491. (b) Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 7876.

(6) (a) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767. (b) Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1996**, *37*, 6315. (c) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (d) Haverlock, T. J.; Mirzadeh, S.; Moyer, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1126. (e) Lee, S. H.; Kim, J. Y.; Ko, J.; Lee, J. Y.; Kim, J. S. *J. Org. Chem.* **2004**, *69*, 2902. (f) Lee, J. Y.; Kwon, J.; Park, C. S.; Lee, J.-E.; Sim, W.; Kim, J. S.; Seo, J.; Yoon, I.; Jung, J. H.; Lee, S. S. *Org. Lett.* **2007**, *9*, 493.

but was able to show an on–off fluorescence cycle when K^+ or Pb^{2+} ion was added sequentially.^{4b}

As part of our continued interest in the design and synthesis of chromogenic⁷ and fluorogenic chemosensors, recently we reported a methodology of attaching isoxazoline or isoxazole units onto the upper or lower rims of calix[4]-arenes by 1,3-dipolar cycloadditions.^{8,9} Here, we report the synthesis of a new fluorescent on–off switchable calix[4]-crown using the Click chemistry¹⁰ of an azide and an alkyne to form a triazole binding site.^{9b}

The synthetic routes for fluorescent sensors **1** and **2** are depicted in Scheme 1. Our synthesis began with the



precursors of 25,27-bis(*O*-propargyl)calix[4]arene **5**¹¹ in the cone conformation. Cyclization of **5** with tetraethyleneglycol ditosylate by using Cs_2CO_3 in MeCN provided **3** in the 1,3-alternate conformation in 35% yield. Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of calix[4]crown **3** with 9-(azidomethyl)anthracene **4** in the Click condition afforded the intense fluorescent 1,2,3-triazole **1** in 82% yield. Compounds **1** and **3** are proven to be in 1,3-alternate conformations because the four methylene bridged carbons in each case showed only one peak in ¹³C NMR spectra.^{9c} The same

(7) Kao, T.-L.; Wang, C.-C.; Pan, Y.-T.; Shiao, Y.-J.; Yen, J.-Y.; Shu, C.-M.; Lee, G.-H.; Peng, S.-M.; Chung, W.-S. *J. Org. Chem.* **2005**, *70*, 2912.

(8) Shiao, Y.-J.; Chiang, P.-C.; Senthilvelan, A.; Tsai, M.-T.; Lee, G.-H.; Chung, W.-S. *Tetrahedron Lett.* **2006**, *47*, 8383.

(9) (a) Senthilvelan, A.; Tsai, M.-T.; Chang, K.-C.; Chung, W.-S. *Tetrahedron Lett.* **2006**, *47*, 9077. (b) To the best of our knowledge, there has been no report heretofore with triazole as a metal ion binding moiety in calix[4]arene related chemosensors. (c) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

(10) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(11) Xu, W.; Vital, J. J.; Puddephatt, R. J. *Can. J. Chem.* **1996**, *74*, 766.

procedures were also employed in the synthesis of compound **2** from 1,3-dimethyl-2-(prop-2-ynoxy)benzene (see the Supporting Information for details). Compound **1** contains both the calix[4]crown and the triazole groups as metal ion binding sites, whereas compound **2** contains only a triazole for metal ion binding.

The fluorescence spectrum of **1** (10 μ M) in MeCN/ $CHCl_3$ (v/v = 1000:4) exhibits a characteristic monomer emission of anthracene with $\lambda_{max} = 415$ nm (excitation at 367 nm), which is very similar to that of **2** (see Figure S9 in the Supporting Information). Using fluorescence spectroscopy as a tool we then screened the metal ion binding abilities of **1** and **2** by comparing the fluorescence intensities of the solutions before and after adding 10 equiv of 15 metal ions as their perchlorate salts: Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Cu^{2+} , Hg^{2+} , Cr^{3+} , Pb^{2+} , Cd^{2+} , Ag^+ , Ni^{2+} , Mn^{2+} , and Zn^{2+} . The results are shown in Figure 1. We found that the

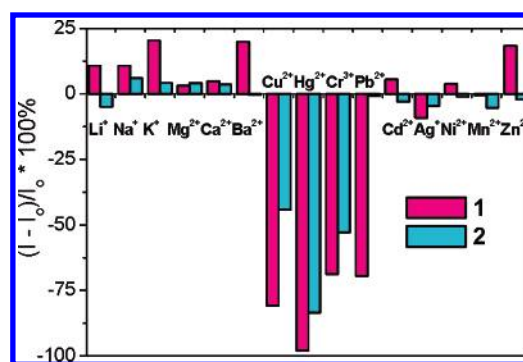


Figure 1. Fluorescence intensity changes ($(I - I_0)/I_0 \times 100\%$) of fluoroionophores **1** and **2** (each of 10 μ M) in MeCN/ $CHCl_3$ (1000:4, v/v) at 298 K upon addition of various metal perchlorates (10 equiv). Excitation wavelength was at 367 nm for **1** and 350 nm for **2**. I_0 is fluorescent emission intensity at 415 nm of each free host, and I is the fluorescent intensity after adding metal ions.

fluorescence of **1** (10 μ M) was strongly quenched by Hg^{2+} , Cu^{2+} , Cr^{3+} , and Pb^{2+} ions; however, it showed enhancement after addition of K^+ , Ba^{2+} , and Zn^{2+} ions. The fluorescence of **2** was also strongly quenched by Hg^{2+} , Cr^{3+} , and Cu^{2+} ions but not by Pb^{2+} . These results suggest that Hg^{2+} , Cu^{2+} , and Cr^{3+} ions can be recognized by the monotriazole group of sensor **2** alone (vide infra for ¹H NMR supports); however, the complexation of Pb^{2+} ion requires the coordination of the two triazole groups of **1**, which leads to a severe fluorescence quenching. The fluorescence quenching of both **1** and **2** may be explained by either a reverse PET¹² or a heavy atom effect.¹³ In the former case, when the Pb^{2+} ion is bound by the two triazole nitrogen atoms, the anthracene units probably behave as PET donors whereas the triazole groups behave as electron acceptors.

(12) (a) Ojida, A.; Mito-oka, Y.; Inoue, M.-A.; Hamachi, I. *J. Am. Chem. Soc.* **2002**, *124*, 6256. (b) de Silva, A. P.; Gunaratne, H. Q. N.; Lynch, P. L. M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 685. (c) Choi, M.; Kim, M.; Lee, K. D.; Han, K.-N.; Yoon, I.-A.; Chung, H.-J.; Yoon, J. *Org. Lett.* **2001**, *3*, 3455.

(13) Chae, M.-Y.; Cherian, X. M.; Czarnik, A. W. *J. Org. Chem.* **1993**, *58*, 5797.

The complexations of Hg^{2+} , Cr^{3+} , and Cu^{2+} ions with **2** are supported by ^1H NMR titration experiments (see Figure S10 in the Supporting Information). In the presence of 1.0 equiv of Hg^{2+} , Cr^{3+} , and Cu^{2+} ions, respectively, chemical shifts of protons H_d – H_f of **2** are significantly downfield shifted; in particular, the peak of H_e on the triazole group is downfield shifted by 0.75, 0.70, and 0.88 ppm, respectively. In contrast, the phenoxy protons H_a and H_b are downfield shifted by only 0.11–0.31 ppm.

The fluorescence spectra of **1** (10 μM) at various concentrations of Pb^{2+} are depicted in Figure 2; as can be seen, no

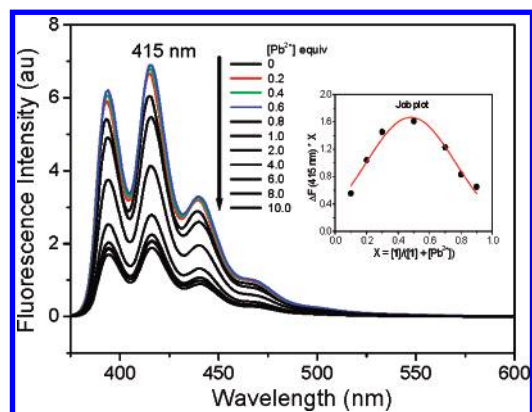


Figure 2. Changes in fluorescence emission spectra of **1** (10 μM) upon titration by Pb^{2+} in $\text{MeCN}/\text{CHCl}_3$ ($v/v = 1000:4$) ($\lambda_{\text{excitation}} = 367$ nm).

shift in the fluorescence maximum was observed. However, the fluorescence intensities of **1** gradually decreased as the concentration of Pb^{2+} increased from 2 to 100 μM . On the basis of the fluorescence intensity of **1** as a function of $[\text{Pb}^{2+}]$, the association constant for $\mathbf{1}\cdot\text{Pb}^{2+}$ in $\text{MeCN}/\text{CHCl}_3$ (1000:4, v/v) was calculated to be $3.71 \times 10^4 \text{ M}^{-1}$ by a Stern–Volmer plot.¹⁴ In the Job plot (see inset of Figure 2),¹⁵ a maximum fluorescence change was observed when the molar fraction of ionophore **1** vs Pb^{2+} was 0.5, indicative of a 1:1 complex. Similar fluorescence titration behavior and a 1:1 binding stoichiometry was also observed in the cases of fluoroionophores **1** and **2** with Hg^{2+} , Cu^{2+} , and Cr^{3+} ions, respectively (see Figures S11–S22 in the Supporting Information for details). From these data, the association constants for complexation of Hg^{2+} , Cu^{2+} , and Cr^{3+} by **1** and **2** were estimated, yielding $\mathbf{1}\cdot\text{Hg}^{2+} = 2.82 \times 10^5 \text{ M}^{-1}$, $\mathbf{1}\cdot\text{Cu}^{2+} = 2.09 \times 10^5 \text{ M}^{-1}$, $\mathbf{1}\cdot\text{Cr}^{3+} = 7.69 \times 10^4 \text{ M}^{-1}$, $\mathbf{2}\cdot\text{Hg}^{2+} = 3.05 \times 10^4 \text{ M}^{-1}$, $\mathbf{2}\cdot\text{Cu}^{2+} = 1.65 \times 10^4 \text{ M}^{-1}$, and $\mathbf{2}\cdot\text{Cr}^{3+} = 2.49 \times 10^4 \text{ M}^{-1}$. In contrast, the addition of 10^{-4} M K^+ to a solution of **1** in $\text{MeCN}/\text{CHCl}_3$ (1000:4, v/v) gave ca. 20% fluorescence enhancement because alkali metal cations are believed to be bound by the calix[4]crown-5 ring.¹⁶

Metal ion-induced chemical shift changes in the ^1H NMR spectra support that the K^+ ion is bound to the crown-5 ring

of **1**; however, Pb^{2+} is mostly bound to the two nitrogen atoms of the triazole groups and partly to the crown-5 unit (see Figure 3). In the presence of 1.0 equiv of K^+ , chemical

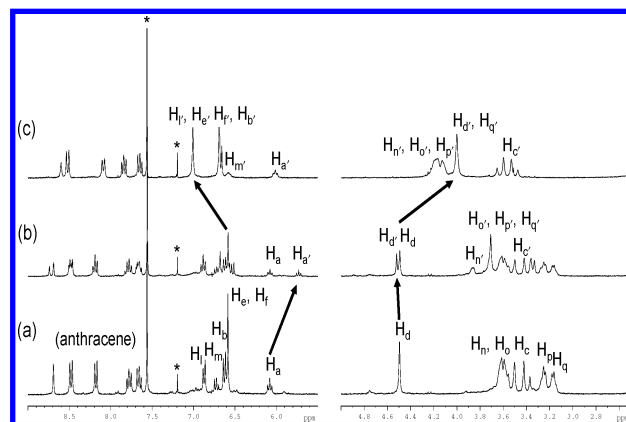


Figure 3. ^1H NMR spectra of **1** (2.5 mM) in a $\text{CDCl}_3/\text{CD}_3\text{CN}$ (3:1) solution (a) and in the presence of 1 equiv of metal perchlorate (b) K^+ and (c) Pb^{2+} , where the asterisk denotes NMR solvent peaks.

shifts of protons H_n – H_q on the crown-5 ring of **1** changed significantly, and the peak of H_a was upfield shifted by 0.34 ppm due to its proximity to the crown-5–metal complex. However, the peak of H_d in the OCH_2 –triazole unit was little influenced, indicating that K^+ is complexed by **1** via the crown ether unit. By contrast, upon adding 1.0 equiv of Pb^{2+} to the solution of **1**, the peak of H_e on the triazole group was downfield shifted by 0.42 ppm and the peak of H_d on the OCH_2 –triazole unit was upfield shifted by 0.50 ppm, suggesting that the two triazole groups are involved in the complexation with Pb^{2+} . Interestingly, the peaks of H_n – H_q on the crown-5 unit of **1** are more downfield shifted in the presence of Pb^{2+} than those in the presence of K^+ , suggesting that the Pb^{2+} ion is also complexed with the crown-5 and the smaller ionic radii of Pb^{2+} compared to K^+ explains^{17c} why H_a did not show much difference in chemical shift.

Selective K^+ binding by the crown-5 ring of the triazole modified calix[4]crown **1** was also proven by an experiment where K^+ was titrated into the $\mathbf{1}\cdot\text{Pb}^{2+}$ complex (vide infra). Since compound **1** contains two different metal ion binding sites, a metal ion will choose the more favorable one when added to the solution of **1**. On the one hand, the two nitrogen atoms of triazole groups of **1** prefer to bind Pb^{2+} ion resulting in a severe fluorescence quenching. On the other hand, the calix[4]crown-5 unit of **1** prefers to bind K^+ ion, which leads to a small fluorescence enhancement. Thus, we observed an interesting off–on switching process when the K^+ ion was added into a solution of $\mathbf{1}\cdot\text{Pb}^{2+}$ (1:10) complex, and the fluorescence intensity was gradually enhanced and reached

(16) Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001; pp 365–384.

(17) (a) Kim, J. S.; Shon, O. J.; Rim, J. A.; Kim, K. S.; Yoon, J. J. *Org. Chem.* **2002**, 67, 2348. (b) Kim, J. S.; Noh, K. H.; Lee, S. H.; Kim, S. K.; Kim, S. K.; Yoon, J. J. *Org. Chem.* **2003**, 68, 597. (c) The ionic radius for K^+ is 1.38 Å and that for Pb^{2+} is 1.19 Å.

(14) For a Stern–Volmer plot please see: Stern, O.; Volmer, M. *Phys. Z.* **1919**, 20, 183.

(15) For a Job plot, please see: Job, P. *Ann. Chim.* **1928**, 9, 113. (b) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

a plateau after adding about 40 equiv (vs Pb^{2+}) of K^+ (see inset of Figure 4). It appears that this metal ion exchange

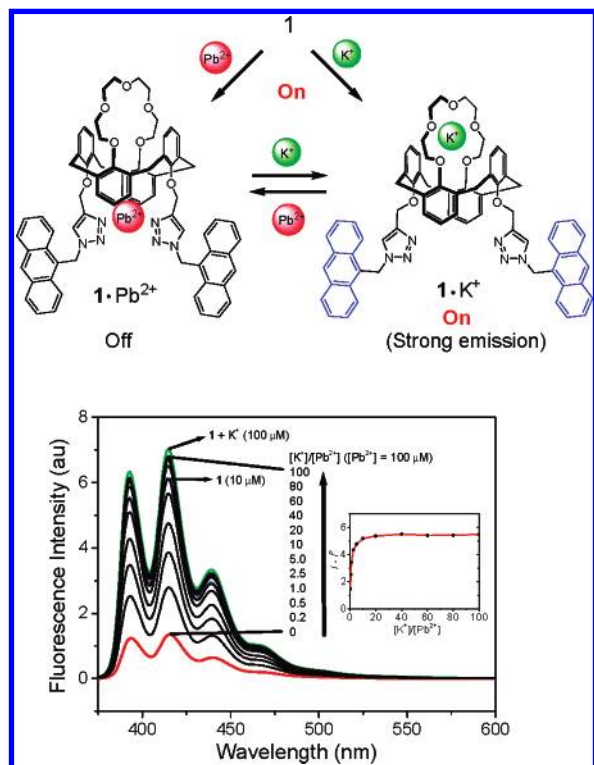


Figure 4. Fluorescence emission changes for the **1** ($10 \mu\text{M}$) with 10 equiv of $\text{Pb}(\text{ClO}_4)_2$ in $\text{MeCN}/\text{CHCl}_3$ ($v/v = 1000:4$) upon addition of various amounts of K^+ ion ($\lambda_{\text{excitation}} = 367 \text{ nm}$).

process is due not only to an electrostatic repulsion¹⁷ between the two metal ions but also to a negative heterotropic allosteric effect.¹⁸ In the reverse of this metal ion exchange process, the Pb^{2+} ion was gradually added into a solution of $\mathbf{1}\cdot\text{K}^+$ (1:10) complex, and the fluorescence intensity was shown to be quenched by the Pb^{2+} ion as shown in Figure 5. Again, metal ion exchange is evident from the gradual decrease of fluorescence intensity where the Pb^{2+} ion moves in and the K^+ ion moves out from **1**.

It should be noted that we were unable to revive the fluorescence intensity of the severely quenched complexes (i.e., $\mathbf{1}\cdot\text{Hg}^{2+}$, $\mathbf{1}\cdot\text{Cu}^{2+}$, and $\mathbf{1}\cdot\text{Cr}^{3+}$) in $\text{MeCN}/\text{CHCl}_3$ ($v/v = 1000:4$) even after the addition of 1000 equiv of K^+ ion (see Figure S23 in the Supporting Information). The results suggest that complexation of K^+ into the crown ether site of **1** could not induce the decomplexation of Hg^{2+} , Cu^{2+} , and Cr^{3+} ions from the triazole site—perhaps the electrostatic repulsion between the two metal ions is not strong enough. Since Hg^{2+} , Cu^{2+} , and Cr^{3+} ions are shown to be recognized by monotriazole **2**, the results in Figure 5 may also imply that no allosteric effect occurred upon addition of K^+ to

(18) (a) Shinkai, S.; Ikeda, M.; Sugasaki, A.; Takeuchi, M. *Acc. Chem. Res.* **2001**, *34*, 494. (b) Takeuchi, M.; Ikeda, M.; Sugasaki, A.; Shinkai, S. *Acc. Chem. Res.* **2001**, *34*, 865. (c) Kovbasyuk, L.; Kramer, R. *Chem. Rev.* **2004**, *104*, 3161.

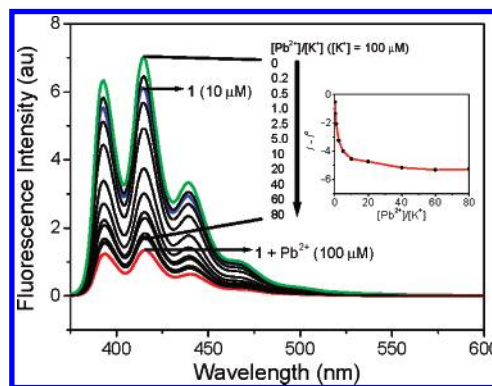


Figure 5. Fluorescence emission changes for the **1** ($10 \mu\text{M}$) with 10 equiv of KClO_4 in $\text{MeCN}/\text{CHCl}_3$ ($v/v = 1000:4$) upon addition of various amounts of Pb^{2+} ion ($\lambda_{\text{excitation}} = 367 \text{ nm}$).

the three metal complexes of **1** (i.e., $\mathbf{1}\cdot\text{Hg}^{2+}$, $\mathbf{1}\cdot\text{Cu}^{2+}$, and $\mathbf{1}\cdot\text{Cr}^{3+}$). We have also carried out experiments using Ba^{2+} and Zn^{2+} ions to affect the fluorescence of $\mathbf{1}\cdot\text{Pb}^{2+}$ and found that K^+ is by far the most efficient cation to revive the fluorescence of **1**. About 20 equiv of K^+ ion (vs Pb^{2+}) is sufficient for the revival of the fluorescence of $\mathbf{1}\cdot\text{Pb}^{2+}$ complex; however, at least 500 equiv of Ba^{2+} or Zn^{2+} is needed to attain a 90% recovery of the fluorescence (see Figures S24 and S25 in the Supporting Information). This suggests that complexation of Ba^{2+} and Zn^{2+} into the crown ether site of **1** is weaker than complexation of **1** with Pb^{2+} in the triazole units. Alternatively, it may imply that Ba^{2+} or Zn^{2+} is more weakly bound to the triazole units of **1** than Pb^{2+} , therefore, they need higher concentrations to compete with the Pb^{2+} ion.

In summary, we have designed a new type of fluorescent chemosensor with two different cationic binding sites on lower rims of a 1,3-alternate calix[4]crown. Furthermore, we have proved that the triazole group(s) can bind metal ions based on both fluorescence spectroscopy and ^1H NMR titration experiments. Upon the addition of Hg^{2+} , Cu^{2+} , Cr^{3+} , or Pb^{2+} ions into a solution of **1** in $\text{MeCN}/\text{CHCl}_3$ (1000:4, v/v), the fluorescence spectrum was strongly quenched because of a reverse PET from the anthracene unit to the triazole group. On the other hand, addition of K^+ to a solution of **1** showed a small enhancement in emission intensity because K^+ is entrapped by the crown-5 unit. Interestingly, the fluorescence of **1** is quenched by Pb^{2+} but can be revived by the addition of excess K^+ ion into the $\mathbf{1}\cdot\text{Pb}^{2+}$ complex. Thus, the metal ion exchange can trigger an on–off switchable fluorescent chemosensor.

Acknowledgment. We thank the National Science Council (NSC) and the MOE ATU Program of the Ministry of Education, Taiwan, Republic of China, for financial support.

Supporting Information Available: Experimental procedures, spectral data of compounds **1–4**, fluorescence emission spectra, and ^1H NMR spectra of **1** and **2** with different metal perchlorates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL071337+